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SURVEY OF LITERATURE RELATING TO INFANT METHEMOGLOBINEMIA DUE TO NITRATE CONTAMINATED WATER

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Environmental Health Center
Cincinnati, Ohio

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INTRODUCTION

Methemoglobinemia is due to the presence of methemoglobin in the blood. It may result from the reaction of any one of several oxidizing agents with the hemoglobin normally present in the blood. Unlike the oxygen in hemoglobin, that in methemoglobin is so firmly bound that the methemoglobin cannot function as an oxygen carrier by alternate oxygenation and deoxygenation. Thus, the result may be anoxemia with serious consequence or even death.

Although methemoglobinemia may result from congenital heart diseases, or from the ingestion, inhalation, or absorption, also from the medicinal administration, of any one of several drugs or chemicals, an important cause of cases in infants is the ingestion of water high in nitrate. This review of the literature is concerned with the latter cause.

HISTORICAL

According to Eusterman and Keith (21), Gangee (28) demonstrated as early as 1868 that the addition of amyl nitrate to blood could result in the formation of methemoglobin. These same authors noted that Binz and Gerlinger (4) reported in 1901 that the administration of large doses of nitrates to animals may cause the formation of methemoglobin. Medovy, Guest and Victor (51) credit Stokivs (68) and Talma (69) with describing cases of methemoglobinemia in 1902.

In reviewing the literature, Comly (13) mentioned that van den Bergh and Gutterink (71) reported in 1906 that nitrites could be formed in the bowels from nitrates, and that the nitrite was more likely to be absorbed if the intestine was damaged. These authors noted a few instances in which a nitrite-producing bacillus was recovered from a stool or sputum of individuals having sulfhemoglobinemia. However, it remained for Zobell (81) to demonstrate in vitro that many organisms commonly found in the gastro-intestinal tract of man are capable of reducing nitrates to nitrites.

In 1928 Barker and O'Hare (3) described a case of cyanosis in a patient who had been treated with ammonium nitrate. The following year, Eusterman and Keith (21) reported two cases of methemoglobinemia which occurred among a large number of adults administered ammonium nitrate for diuretic purposes. However, after two dogs, to which they administered intravenous injections of the drug, failed to show symptoms

of methemoglobinemia, they concluded these cases were due to abnormal metabolic processes in the two patients. In 1933, Roe (60) reported the death of a month-old infant who had been treated with bismuth subnitrate. He was the first to associate nitrates with serious or even fatal cases of infant methemoglobinemia. One year later Chen, Rose and Clowes (12) demonstrated that methemoglobinemia could be produced by intravenous injections of sodium nitrate.

Thus, the way was paved for Comly (13), who in reporting on two cases of infant methemoglobinemia in 1945, concluded that methemoglobinemia may occur in an infant following ingestion of water high in nitrates, especially if the infant is suffering from gastro-intestinal disturbances. Maxcy (47), writing in 1950, noted that subsequent observations have established the validity of Dr. Comly's hypothesis.

MEDICAL ASPECTS

Cause. Although methemoglobinemia in infants may be caused by congenital heart diseases (13) (20) (21), by absorption of dyes used for laundry marking (31) (61) (78), and by drugs administered in medical treatment (60) (76), many of the cases reported since 1945, when Comly (13) published his conclusions that infant methemoglobinemia may be due to ingestion of high nitrate water, have been diagnosed as having been due to nitrates in the water used in the feeding formula (8) (11) (23) (24) (48) (50) (59) (66) (84) (85). Donahue (18) alone has expressed the belief that infant methemoglobinemia may result from nitrates ingested in the mother's or cow's milk. However, no positive test for nitrates could be demonstrated in the milk from two cows fed for a period of 10 days on water containing 114 p.p.m. nitrate nitrogen (83).

Susceptibility. Comly's hypothesis on infant methemoglobinemia induced by ingestion of high nitrate water caused considerable speculation concerning the effect of age and other factors on susceptibility. This led to a series of experiments conducted by Cornblath and Hartman (15). They fed several infants on a formula containing an artificial well water of high nitrate nitrogen concentration, but failed to produce apparent methemoglobinemia. Further investigation revealed that nitrate reducing organisms, which they cultured from saliva and gastric juices of infant cases, were active only at a pH level above 4.9. On checking the gastric juices of infants, who previously had developed appreciable levels of methemoglobin, they found no free acid and pH values above 4. Based on this evidence Cornblath and Hartmann concluded that the lack of acidity of the gastric juices of a newly born infant may permit nitrate reducing organisms to grow in the upper gastro-intestinal tract and, thus, to reduce nitrates to nitrites before the former can be completely absorbed. In an older infant the acidity of the gastric juices inhibits the growth of the nitrate reducing bacteria.

The work of Harriott, Hartmann and Levin (45), who investigated the acidity and bacterial flora of 200 infants suffering diarrhea, supports this hypothesis. The pH of the stomach contents of well infants varied from 2.0 to 5.0, and averaged 3.7; that for infants suffering from bacillary dysentery ranged from 2.0 to 5.0, and averaged 3.0; but that for infants with non-specified diarrhea averaged 5.6, and varied from 4.6 to 6.5.

Robertson and Riddell (59) considered the total amount of hemoglobin present in the blood and the energy of the enzyme system which operates to reduce methemoglobin to hemoglobin important. Several observers (13) (61) (71) have suggested that the nitrite formed in the upper gastro-intestinal tract is more readily absorbed into the blood system when the mucosa is damaged.

In an analysis of 94 cases, Bosch, et al. (8), noted the period of exposure to a feeding formula containing high nitrate water varied from 1 to 30 or more days.

Apparently, some of the factors which determine whether or not an infant may have nitrate induced methemoglobinemia are: (a) nitrate nitrogen content and amount of water ingested daily; (b) the duration of exposure to a feeding formula containing high nitrate water; (c) the presence and activity of nitrate reducing bacteria in the upper gastro-intestinal tract - which is affected by the pH of the gastric juices; and (4) the condition of the mucosa.

Physiological Effects. The characteristic symptoms ordinarily associated with infant methemoglobinemia are the greyish or brownish blue coloration, which usually is first noticeable around the lips, spreads to the fingers and toes and over the face, and may eventually cover the entire body (8). Other symptoms which may be noticed are drowsiness and an increased rate of respiration (48). Although not always present, methemoglobinemia is commonly accompanied by diarrhea or other gastro-intestinal distrubances (10).

The cyanosis - the greyish or brownish blue coloration - is attributed to the anoxemia resulting from the decrease in the oxygen transporting capacity of the blood (26). The nitrites, absorbed by the blood, react with the hemoglobin to form methemoglobin. Conant (14) notes that this is an oxidation reaction in which the ferrous iron in hemoglobin is oxidized to ferric iron in methemoglobin. In the latter state the oxygen is so firmly bound that methemoglobin cannot function in the manner of hemoglobin in the transfer of oxygen. Ordinarily this reaction is reversible and occurs without permanent injury to the red blood cells.

According to Robertson and Riddell (59), methemoglobinemia is usually first noticeable in infants when 10 per cent of the hemoglobin has been transformed to methemoglobin, and severe cases may result when it increases to 20 per cent. However, recovery has occurred in cases where the methemoglobin level has been observed to be as high as 57 per cent (64).

Diagnosis. Diagnosis of cases of infant methemoglobinemia as being due to the ingestion of nitrate contaminated water may be either presumptive or absolute. According to Bosch, et al. (8), a presumptive diagnosis is justified when the physical findings are typical and either the freshly removed blood has the chocolate brown color associated with methemoglobin, or spontaneous disappearance of the cyanotic condition occurs within 48 hours after changing the water used in the feeding formula, provided an analysis of the water originally used in the feeding formula shows it to have a nitrate-nitrogen content in excess of 10 or 20 p.p.m.

An absolute diagnosis requires the demonstration of appreciable amounts of methemoglobin in the blood by either a spectroscopic examination or the photoelectric colorimetric method of Evelyn and Malloy (22), together with analytical results showing at least 10 or 20 p.p.m. of nitrate nitrogen in the water used in the feeding formula. Finch (26) cautions that the blood should be examined within 1 or 2 hours after withdrawal since on standing methemoglobin may be spontaneously reduced to hemoglobin.

Treatment. In general, treatment of infants having nitrate water induced methemoglobin has consisted of the discontinuance of the use of nitrate contaminated water and, in the more severe cases, the intravenous injection or oral administration of methylene blue. Oxygen therapy, also the administration of such drugs as ascorbic acid, thiamine, and niacin, have been used, but for one reason or another none of these treatments has found general use.

In cases where a water of permissible nitrate content could not be obtained, Comly (13) recommended feeding whole milk, preferably acidified and boiled. Stafford (66) suggested the new born infant be retained in a hospital until the safety of the water to be used in the feeding formula has been determined.

Various observers (29) (51) (66) have reported the recovery of infant methemoglobinemia cases following the change from use of nitrate contaminated water to one relatively free from nitrates. In several instances an infant has again become cyanotic when returned to his original feeding formula containing high nitrate water (13) (61) (66). Bosch, et al. (8) implied that spontaneous recovery should occur in 48 hours after discontinuance of use of a feeding formula containing high nitrate water, while Halpen and Dubost (33) stated that such recovery will occur in 4 days.

In 1939, prior to Comly's hypothesis of high nitrate water induced methemoglobinemia, Wendel (79) reported on the effectiveness of methylene blue in treating sodium nitrite induced methemoglobinemia in dogs. He found that an intravenous injection of 0.1 to 0.2 cc. of a 1 per cent solution (1 to 2 mg.) of methylene blue per kilogram of body weight resulted in a rapid decrease in the methemoglobin level. In studying the molecular ratio of the hemoglobin produced per unit of methylene blue added, he could not explain the reaction

on the basis of the reducing action of methylene blue. Thus, he concluded that it was a catalyst which accelerated the rate with which the enzyme systems of the red cells normally reduced methemoglobin to hemoglobin.

Warburg, et al. (74), according to Stafford (66), found an overdose of methylene blue may produce methemoglobinemia. However, Finch (26) does not consider this important, since dosages up to 10 mg. per kilogram of body weight do not produce significant amounts of methemoglobin. It is at least significant that intravenous injections of 1 to 2 mg. per kilogram of body weight have resulted in the disappearance of cyanotic conditions in numerous cases in a matter of 30 minutes or less (11) (13) (23) (24).

In his studies, Wendel (79) also noted that oral administration was effective. Stafford (66) stated the dosage used in oral administration should be 10 to 20 mg. of methylene blue per kilogram of body weight. This is about 10 times the amount used in intravenous injections. He reported favorable results following treatment by oral administration.

Prevention. In general, the prevention of infant methemoglobinemia due to nitrate contaminated water is largely one of education. If the infant's parents and the doctor in the case are informed of the problem, steps are usually taken to prevent nitrate induced methemoglobinemia.

Water for use in preparing the infant's formula should contain not more than 10 or possibly 20 p.p.m. nitrate nitrogen (13) (47). In areas where there is the least question concerning the nitrate content of the water to be used, a sample of that water should be taken and analyzed. If it is high in nitrates, the infant should be retained at the hospital (66), the feeding should be whole milk without addition of any water (13), or water having a safe nitrate concentration should be obtained and used in preparing the formula.

An intensive program has resulted in a marked decrease in the reported cases. For example in Minnesota the reported cases were 55 in 1947, 52 in 1948, but only 12 for the first six months of 1949 (8).

In some cases it may be possible to secure a low nitrate water by constructing new wells, properly located and protected from surface contamination. However, this problem appears to require further investigation.

Finally, reporting of methemoglobinemia in infants should be required. Information on the extent of the cases and the regions in which they occur would prove helpful in its prevention.

MORBIDITY AND MORTALITY

Metzler (52) noted that methemoglobinemia is not one of the reportable diseases; and that the cases voluntarily reported are a poor indication of the incidence. The most complete information on the morbidity and mortality among infants due to methemoglobinemia resulting from ingestion of nitrate contaminated water is the summary of reported cases and deaths included in the report of the Committee on Water Supply, Engineering Section, American Public Health Association (89). Table I reproduces in part that data. It is based on a questionnaire sent to the 48 states and Alaska and Hawaii, to which all but one state replied. Special emphasis was placed on restricting the data to those cases definitely associated with nitrate contaminated water. Apparently, the reported cases cover a period from 1945, or even earlier, to the dates of the replies to the questionnaires.

A total of over 278 cases and of 39 deaths are noted. Geographically the states reporting cases center around Iowa, where the first case associated with nitrate contaminated water was recognized. Except for the north central group, only 4 states - California, Georgia, New York and Virginia - reported cases. Infant methemoglobinemia due to high nitrate waters has also been reported for Canada (50)(59) and Belgium (24).

Probably the most intensive study of nitrate induced infant methemoglobinemia is that for Minnesota, which was reported by Bosch et al. (8). It is interesting to note that familiarity with the problem by both physicians and parents apparently has led to a marked decrease in the reported cases.

WATER SUPPLY ASPECTS

Permissible Nitrate Nitrogen Concentration. The permissible nitrate nitrogen concentration in water which may cause infant methemoglobinemia when used in a feeding formula is dependent on the individual's susceptibility, the increase in nitrate nitrogen concentration due to boiling the water, the quantity of boiled water consumed per day per unit weight of the infant, the duration of exposure to the high nitrate water, and possibly other factors (8) (15) (47).

Comly (13) considered it inadvisable to use well water containing more than 10 or 20 p.p.m. nitrate nitrogen in preparing an infant's feeding formula. Data presented in Table II indicate no cases were reported which were associated with water containing 10 p.p.m. nitrate nitrogen or less, and the nitrate nitrogen content was less than 20 p.p.m. for only 2.3 per cent of the cases for which data were available. It should be noted, however, that in many of these cases clinical data were insufficient for definite diagnosis, and samples of water for the analysis were sometimes collected several months following the occurrence of the case.

TABLE I

REPORTED CASES OF NITRATE WATER INDUCED INFANT METHEMOGLOBINEMIA
CLASSIFIED ACCORDING TO NITRATE-NITROGEN CONCENTRATION OF WATER USED IN FEEDING FORMULA

STATE	METHEMOGLOBINEMIA		NUMBER OF CASES ASSOCIATED WITH INDICATED RANGES OF NO_3-N CONC. (PPM)						NO. OF CASES FOR WHICH DATA ARE AVAILABLE	SUPPLEMENTARY REFERENCE
	Reported Cases	Reported Deaths	0-10	11-20	21-30	31-50	51-100	100+		
California	1	0	0	0	0	0	1	0	1	
Georgia	6	3	-	-	-	-	-	-	0	Frith (27)
Illinois	75	6	0	1	2	2	12	11	28	
Indiana	1	0	0	0	0	0	1	0	1	
Iowa	Several	11	0	0	0	0	1	1	2	
Kansas	13	3	0	0	1	1	2	8	12	Metzler (52)
Michigan	7	0	0	0	0	0	0	7	7	
Minnesota	139	14	0	2	25		53	49	129	Bosch et al. (8)
Missouri	2	0	0	0	0	0	0	2	2	
Nebraska	22	1	0	1	0	4	9	8	22	
New York	2	0	0	0	0	0	1	0	1	
North Dakota	9	1	0	1	1	0	0	6	8	
Ohio	0	0	0	0	0	0	0	0	0	
Oklahoma	0	0	0	0	0	0	0	0	0	
South Dakota	Several	0	-	-	-	-	-	-	-	
Texas	0	0	0	0	0	0	0	0	0	
Virginia	1	0	0	0	0	0	1	0	0	
	278+	39	0	5	36		80	92	213	
Percent of total			0.0	2.3	16.9		37.6	43.2	100.0	

Principal Source: Progress Report of Committee on Water Supply, A.P.H.A., "Water Supply: Nitrate in Potable Waters and Methemoglobinemia". A.J.P.H. 1949-50 Yearbook, 40 (Part II),. 111 (May, 1950).

TABLE II

HIGH NITRATE WATERS, THEIR GEOGRAPHICAL DISTRIBUTION AND RELATION TO REPORTED CASES OF INFANT METHEMOGLOBINEMIA

State	Total No. Methemo. Cases Reported	Year	Type of Supply	No. of samples examined	Percent of Samples Examined within indicated NO_3-N (PPM) Range				Reference
					0-10	11-20	21-50	50+	
California	1	-	-	-	-	-	-	-	
Georgia	6	-	-	-	-	-	-	-	
Illinois	75	1946		7000	80±	← 20± →			(76)
Indiana	1	-	-	146	← 98.7 →	← 1.3 →			(52)
Iowa	69	1939	Dug Wells	454	66.5	10.6	14.3	8.6	(38)
			Drilled Wells	647	95.5	2.5	1.5	0.4	
			Bored Wells	278	70.4	7.9	7.1	5.4	
		1943	Dug Wells	243	48.5	11.1	12.4	28.0	
			Private Wells,						
			< 100'd	1943	← 72± →		← 28± →		(7)
			> 100	370	← 96 1/2 →		← 3 1/2 →		
Kansas	13	-	Rural Wells	-	67±	← 33± →			(52)
Massachusetts	0	1948	Private	?	?	← 47 samples →			(89)
Michigan	7	-	-	2847	93	← 7 →			(48)
Minnesota	139	1947-9	Municipal	514	96.9	← 3.0 →			(8)
				2912	84.9	← 15.1 →			
Missouri	2	-	-	-	-	-	-	-	
Nebraska	22	1948-9	Municipal	416	95.0	← 5.0 →			(83)
			Non-municipal	2687	79.8	← 20.2 →			
			School	258	95.0	← 5.0 →			
			Farm	275	78.0	← 22.0 →			
New York	2	1943	-	2864	96.1	3.3	0.6	0.0	(89)
		1944	-	3528	96.9	2.5	0.6	0.0	
		1945	-	5117	97.4	1.8	0.7	0.1	
		1946	-	6524	96.4	2.1	1.3	0.2	
North Dakota	9	-	-	509	84.9	← 15.1 →			(1)
	-		-	287	84.0	← 16.0 →			(72)
Ohio	0		Rural Wells	10,500	90.5	5.0	3.5	1.0	(75)
			State Park Wells	400	100.0	0.0	0.0	0.0	
Oklahoma	0	-	-	415	Av. NO_3-N Conc. = 28 p.p.m.				(89)
South Dakota	Sev.	-	-	-	-	-	-	-	
Texas	0	-	Rural Wells		Numerous				(89)
Virginia	1	-	Rural Wells	-	-	-	-	-	

Although 10 p.p.m. nitrate nitrogen has been suggested as the permissible level (13) (47), the A.P.H.A. Committee (89) points out that most of the cases studied were associated with nitrate nitrogen concentration in excess of 40 p.p.m. and comments that it is "impossible at this time to select any precise concentration of nitrates in potable waters fed infants which definitely will distinguish between waters which are safe or unsafe ...".

Geographical Distribution. The geographical distribution of high nitrate waters is widespread. Twenty of 37 states, which replied to this item on the A.P.H.A. Committee's questionnaire, reported wells yielding water containing in excess of 50 p.p.m. nitrate nitrogen (89). Results of fairly extensive surveys, indicating the occurrence and concentrations of high nitrate waters, are available in the literature for Illinois (79), Iowa (38), Michigan (48), Minnesota (8), Nebraska (83), New York (89), and Ohio (78). The available data are summarized in Table II.

Although the information presented in the literature is insufficient to permit a sound analysis of the problem, it does indicate that waters of high nitrate nitrogen concentration occur in a sufficient number of instances to anticipate cases of nitrate water induced methemoglobinemia in Illinois, Iowa, Michigan, Minnesota, Nebraska, Ohio, Oklahoma and possibly New York and Texas. The absence of any reported cases of infant methemoglobinemia in Ohio, Oklahoma, and possibly Texas, does not appear to be due to the lack of occurrence of high nitrate waters.

Types of Supply. High nitrate waters have been found most frequently in private wells serving rural homes. However, water containing in excess of 10 p.p.m. nitrate nitrogen has been reported for wells supplying municipal water works in Illinois (49) (79), Kansas (52), Minnesota (8), Nebraska (83) and New York (89). Available evidence indicates surface supplies do not offer a problem except in very unusual cases (78) (89) (49).

Construction of Wells. Most cases of infant methemoglobinemia have been associated with water from dug wells. Bosch et al. (8) noted that in 125 of 129 cases investigated the water came from dug wells. Data reported for Iowa (38) show nitrate nitrogen concentrations over 10 p.p.m. were found in water samples from 39.7 per cent of the dug wells, 21.5 per cent of the bored wells, and only 4.5 per cent of the drilled wells.

The location and physical features, also the nature of the water-bearing strata, may be important. Nearby sources of pollution were believed to be significant by 12 of 22 states reporting on this item in the A.P.H.A. Committee's questionnaire (89). Bosch et al. (8) noted that 83 of 129 wells involved in cases of methemoglobinemia were within less than 50 feet from a barnyard, pigpen, privy, cesspool or other sources of animal or human contamination. It may be significant to note the marked difference, shown in Table II, in the percentage

of high nitrate waters from school and farm wells in Nebraska, also that between state park wells and rural wells in Ohio

In many cases farm wells, and particularly dug wells, are inadequately protected against contamination by surface water or water percolating but a short distance through the soil. Thus, as might be expected, several states have reported a high percentage of the high nitrate waters to be positive for coliform organisms (38) (59) (75) (76). However, there appears to be no relationship between nitrate concentration and bacterial numbers.

Sources of Nitrate Contamination. According to Sarles et al. (63) the principal sources of nitrogenous matter in the soil are the decomposition products of plants, animals and microorganisms; the liquid and solid wastes of animal metabolism; and fertilizers added to enrich the soil. The possibility of geological formations containing appreciable amounts of nitrates must also be considered.

It may be significant that 12 of 22 states replying to this item on the A.P.H.A. Committee's questionnaire expressed the opinion that nearby sources - barnyards, pigpens, privies, cesspools, etc. - were important in causing high nitrate waters (89). Such a belief is substantiated by the variation in nitrate nitrogen content of waters from wells, such as noted by Borts (7), Maxey (47), and in the New York studies (89). However, Metzler (52) observed only seasonal change in the nitrate content of 4 municipal wells, and Bosch et al. (8) noted no appreciable variation in the nitrate content of samples taken bi-weekly from each of 5 wells, or in samples from 2 wells taken after more than an hour continuous pumping. Two wells, a 30 foot dug well and a 71 foot drilled well, were reconstructed in an attempt to exclude nitrate contamination, but no significant reductions in the nitrate content of their waters were noted.

The A.P.H.A. Committee report (89) notes that high concentration of nitrates in waters in rural wells, which usually were poorly constructed, shallow, dug wells, did not seem to be associated with nearby sources of pollution. Weart (76) notes that the upper 40 inches of soil may contain 16,000 lbs. of organic nitrogen per acre. Sarles, Frazier, and McCarter (63) discuss the decomposition of nitrogenous matter. Proteins and nitrogenous matter are first hydrolyzed into amino acids or other water-soluble products consumed by bacteria which give off ammonia. Nitrification may occur through the action of Nitrosomonas or Nitrosococcus bacteria, which in the presence of air oxidize ammonia to nitrous acid; and by Nitrobacter, which oxidize the nitrous acid to nitric acid.

Since bacteria are essential in the production of nitrates from organic nitrogen, factors influencing their activity affect the nitrate content of the soil. Sarles et al. (63) note that nitrification takes place only when the soil contains buffering substances which neutralize the nitric acid and maintain a pH around

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6.5 to 8.0; when aerobic conditions, such as result from plowing, cultivating, etc., are maintained; when soil contains only about 50 per cent of its water-holding capacity; when ammonia salts and other nutrient elements are present in the soil; and at temperatures above 50° and below 100° F.

ANALYTICAL PROCEDURES

There are several procedures by which the nitrate content of water may be determined. Most laboratories use a screening test to differentiate between low and high nitrate concentrations, and then determine the nitrate-nitrogen in high nitrate waters by a more accurate procedure.

One nitrate screening test is that developed by Riehl (75), which he adopted from "Qualitative Analysis by Spot Tests" by Fritz Feigl. Another screening procedure is that developed by Bray (9) and used by Illinois. Both of these procedures are spot plate tests which may be used in the field to prevent overburdening the laboratory with large numbers of samples of low-nitrate waters.

Metzler (52) reports that the brucine procedure is used in Kansas. Local health departments have been equipped with field test kits with which on-the-spot tests are made to determine whether the nitrate nitrogen concentration is within the 10 p.p.m. limit usually considered the maximum permissible level.

More precise methods for use in the laboratory are the phenol-disulfonic acid and reduction methods as given in Standard Methods (88). Still another method which can be used is the Brucine method (36) (55) (80). For precise work it would seem desirable to use a photoelectric colorimeter for comparing the color developed in samples with that of standard concentrations.

FURTHER INVESTIGATIONS NEEDED

Maxcy (47), in a report adopted by the Committee on Sanitary Engineering and Environment, Division of Medical Sciences, National Research Council, notes that there is urgent need for further study before comprehensive measures of prevention can be advocated. Such a study should consist of observations in the various parts of the United States by the same unit.

Some of the factors which should be investigated are the permissible level of nitrates in waters fed infants; the factors which predispose some infants to methemoglobinemia, whereas other infants consuming equally high nitrate waters are unaffected; the health of infants routinely consuming water containing high nitrate in regions where methemoglobinemia has not been reported; the fluctuations, if any, in the nitrate content of waters from selected wells, including factors which influence such variations (47) (89).

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REFERENCE LISTED ACCORDING TO SUBJECT MATTER

(Numbers refer to numbered references in main reference list)

HISTORICAL

3 4 12 13 21 28 41 47
51 60 68 69 71 81

MEDICAL

Cause

8 11 13 18 20 23 24 31
48 50 53 58 59 60 61 66
73 78 84 85

Susceptibility

7 8 13 15 45 46 56 61

Diagnosis

8 21 26

Treatment

5 8 11 13 23 24 25 26
33 34 35 37 41 51 54 61
66 74

Prevention

8 13 47 52 66

MORBIDITY AND MORTALITY

8 27 47 52 83 89

WATER SUPPLY ASPECTS

Critical Nitrate Nitrogen Level

13 15 47

Geographical Distribution

1 8 17 30 52 83 89

Types of Supplies

8 47 75 83 89

Well Construction

7 8 47 52 75 76 89

Sources of Nitrates

7 8 44 52 63 75 76

ANALYTICAL PROCEDURES

9 39 40 57 65 75 88

FURTHER INVESTIGATIONS NEEDED

47 89